Alzheimer's-Related Peptide Amyloid-beta Plays a Conserved Role in Angiogenesis.

Journal: PLoS One

Publication Year: 2012

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PubMed link: 22792182

Funding Grants: ES-Derived Cells for the Treatment of Alzheimer's Disease

Public Summary:
Alzheimer's disease affects over 5 million people in the USA. Although deposits of the peptide amyloid-beta are a critical feature of the pathology, the normal physiological role of this peptide remains unclear. In this publication we show that amyloid-beta plays a role in blood vessel density within the brain. This point is significant to understanding Alzheimer's disease because the brain deposits of amyloid-beta, commonly known as plaques, are surrounded by tissue that has very dense blood vessel networks, aka as hyper-vascular. Some of those vessels form loops and dead ends that are inefficient at providing a proper blood supply to cells in those areas. As an allegory, we suggest it is like adding extra sprinklers to a green lawn: while ten sprinklers might work well a hundred could result in only trickles from branch with brown (under-nourished) patches in between – where Alzheimer's pathology can take hold and eventually form plaques. Findings from this study help us understand how monomeric Aβ affects local blood vessel density, which may be an early event in Alzheimer's etiology. Knowledge arising from this research will contribute to the development of new and effective therapies for this terrible disease. CIRM-funded research supported group interactions in Dr. Ethell's laboratory that contributed to this breakthrough, and helped defray costs of publication.

Scientific Abstract:
Alzheimer's disease research has been at an impasse in recent years with lingering questions about the involvement of Amyloid-beta (Abeta). Early versions of the amyloid hypothesis considered Abeta something of an undesirable byproduct of APP processing that wreaks havoc on the human neocortex, yet evolutionary conservation - over three hundred million years - indicates this peptide plays an important biological role in survival and reproductive fitness. Here we describe how Abeta regulates blood vessel branching in tissues as varied as human umbilical vein and zebrafish hindbrain. High physiological concentrations of Abeta monomer induced angiogenesis by a conserved mechanism that blocks gamma-secretase processing of a Notch intermediate, NEXT, and reduces the expression of downstream Notch target genes. Our findings allude to an integration of signaling pathways that utilize gamma-secretase activity, which may have significant implications for our understanding of Alzheimer's pathogenesis vis-a-vis vascular changes that set the stage for ensuing neurodegeneration.